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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,579	09/07/1999	SUSUMU IKEHARA	Q55691	2802

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/380,579	**Applicant(s)** IKEHARA ET AL.	
	Examiner Michail A. Belyavskyi	**Art Unit** 1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 22 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *9 and 10*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because: Claims 9 and 10 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

" engraftment rate of 100 % for more than 13 weeks " claimed in 9 represent a departure from the specification and the claims as originally filed. The passages pointed by the applicant do not provide a clear support for the general term "over a period of for more than 13 weeks". The specification and the claims as originally field only support " engraftment rate of 100 % up to 13 week.

Applicant's arguments filed 06/22/07 have been fully considered, but have not been found convincing.

Applicant's asserts that the expression "more than 13 weeks" is supported the at page 28, lines 10-16 of the Specification.

Contrary to Applicant's assertion, the Specification on page 28, lines 10-16 explicitly disclosed that " successful engraftment was obtained in 3 of 3 recipient mice in the portal administration group at week 13 after transplantation" (emphases added). It is the Examiner position, that said teaching of the Specification only supports " engraftment rate of 100 % up to 13 week , not more than 13 weeks

2. Claims 9-10 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,428,782 in view of US Patent. No. 5,514,364, Zhang et al. (Eur. J. Immunol. 24 :1558-1565, IDS) and US Patent 5,876708 for the same reasons set forth in the previous Office Action mailed on 02/22/07.

Applicant's arguments, filed 06/22/07 have been fully considered, but have not been found convincing.

Applicant asserts that: the Examiner overlooked Applicant's arguments that there is no motivation or suggestion in prior art references to combine the teaching.

Contrary to Applicant's assertion, it has been recently stated that KSR forecloses the argument that a specific teaching, suggestion, or motivation are required to support a finding of obviousness See Board decision (see KSR International Co v Teleflex Inc., 550U.S.-, 82 USPQ2d 1385, 2007).

As was stated in the previous Office Action, it is the Examiner position, that US Patent '782 teaches a method for reducing graft rejection in an organ transplantation recipient by subjecting the recipient to sublethal total body irradiation (TBI) and administering to the recipient whole bone marrow. Applicants attention is respectfully directed to column 8, lines 57-67, where it is specifically stated that " if TBI is used it should be at a dose level that causes no servere or irreversible pancytopenia. US Patent '782 teaches that transplanting of organ into recipient occurs within the same day as whole bone cells are administered (see column 13, lines 50-67, column 14, lines 10-15 and Example 14 in particular). US Patent '782 teaches that engraftment rate of 100 % is achieved (see Fig, 5, 7, 17, 20, Tables I -III example 14 in particular). Moreover, the Examiner disagree with Applicant in that "based on the data presented in US Patent '782 a person skilled in the art could not predict an engraftmernt rate of 100". The data presented in Fig. 4 and 7 only shown cumulative data from experiments to determine the GVL activity across an incompatibility involving both MHC and MiHL alloantigens. The Specification in Table 1-3 disclosed data that skin allografts survived for more than 100 days in all mice. In Example 14, it is explicitly stated that 100% of BM stromal grafts and approximately 80 % of the heart graft survived. However, it is further disclosed that by simply altering doses of treatment , including doses of radiation, might be beneficial to achieve better engraftment (emphases added).

With regards to the statement that a person skilled in the art would expect the same level of effects as achieved by US Patent '782. As has been acknowledge by Applicant, TBI taught by US Patent '782 was conducted at dose of 4.0 Gy which is much less than claimed in the present invention. Thus skilled artisan could appreciate that a higher dose of TBI might be beneficial and would result in higher engraftment rate, as taught by US Patent '708.

With regards to Applicant statement that "in view of Fig.2 of US Patent '782 wherein increasing the dose of irradiation reduces survival a person skilled in the art would never think of increasing the dose of TBI in the method disclosed in US Patent' 782".
The data presented in Fig.2 was obtained using TLI irradiation, not TBI . Clearly one skill in the art would know the difference between these two treatments. Moreover, skilled artisan could appreciate that a higher dose of TBI might be beneficial as taught by US Patent '708.
In addition, US Patent'364 explicitly teaches that the dose of TBI administered directly correlates with the engraftment rate. At doses below 6.0 Gy less than 50 % engraftment can be achieved, however, increasing the doses up to 7.0 Gy results in 100% ingraftment (see column 17, lines 5-25 in particular). It is the Examiner position that at the time the invention was made one skilled in the art would thinks of increasing the dose of TBI in the method disclosed in US Patent'782.

US Patent '782 does not teaches the sublethal total body irradiation of at least 6.5 Gy or 6.5 Gy to 7.0 Gy , or that said irradiation is performed one day prior to administration of whole bone marrow cells (newly claimed in claim 9), or administering of whole bone marrow cells by hepatic portal administration.

US Patent '364 teaches and claims a method of conditioning of a recipient intended for organ grafting by subjecting the recipient to sublethal total body irradiation and administering to the recipient whole bone marrow (see entire document, but especially the claims and columns 5, 8, 17 and 21-22). Applicant's attention is respectfully directed to column 9, lines 15-20 where it is explicitly stated that " the importance of the hematopoietic niches or "space" contributed by the low dose of TBI is even more evident when TBI is given one week prior to bone marrow transplantation...". Clearly one skill in the art would interpret said statement as an evidence of the advantage of using TBI .

With respect to the issue that US Patent '364 relates to a technique using mixed chimerism not allogenic chimerism. Applicant's attention is respectfully directed to column 9, line 5-10 and column 19, lines 15-45, wherein it is clearly stated that US Patent '364 invention uses allogenic chemerism as well. Moreover, US Patent '364 also teaches that bone marrow engraftment after sublethal total body irradiation is reliably achieved in 100% of recipients at 7.0 Gy (see Figure 1 and column 17, especially lines 4-25). With regards to Applicant's comments that Fig.7 does not show a 100% acceptance of skin grafts after 19 days. Applicant's attention is respectively drawn to Fig.7 for date on B10, wherein 100% engraftment rate has been achieved beyond day 19. It is noted that the US Patent '364 teaches that grafts were followed for a minimum of 35 days. There are no data that shows that after that time grafts were rejected. Moreover, Applicant's attention is respectively drawn column 17, lines 5-25. It is explicitly disclosed that allogeneic engraftment was reliably achieved in 100 %. US '364 further teaches transplantation of organs to the bone marrow recipient and exemplifies skin transplantation, showing that the recipients are specifically tolerant of the donor-type skin (see e.g., Abstract and columns 21-22).

Zhang et al. teach that in both intravenous and portal vein injections of bone marrow cells (BMC), most of the cells migrate to the liver, although more BMC do so after portal vein administration than after intravenous administration (see entire document, especially Figures 3 and 5 and page 1563 at the 4th full paragraph). Zhang et al. also review the art recognized prolongation of organ graft survival in a recipient when cells from the donor are administered to the recipient via the portal vein in addition to the transplanted organ, and note that this is due to a form of immunological tolerance (see especially the "Introduction" on page 1558 and the 1st paragraph of "Discussion" on page 1563).

US Patent '708 teaches a method of inducing immunological tolerance in an organ transplantation recipient, including a step of subjecting the recipient to total body irradiation (TBI) prior to administering to the recipient tolerogen effective amount of bone marrow cells(BMC) (see entire document, Abstract and column 1, lines 25-45, column 3, lines 45-60 and column 9, lines 1-10 in particular). US Patent '708 teaches that said total body irradiation can be performed one day prior to administration of bone marrow cells (see column 9, lines 5-65, column 38, lines 25-60 in particular). US '708 teaches that administration of TBI one day prior to administering BMC is necessary to eliminate recipient's endogenous BMC to stimulate hematopoiesis of the newly introduced foreign BMC.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '364, US Patent '708 and Zhang et al., to those of US Patent '782 to obtain a claimed method comprising administering to an organ transplant recipient total body sublethal irradiation of at least 6.5 Gy or 6.5 Gy to 7.0 Gy, wherein said irradiation is performed one day prior to administration of whole bone marrow cells and administering whole bone marrow cells by hepatic portal administration.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine sublethal TBI about 7.0 Gy as taught by US Patent '364 and performing said irradiation one day prior to administration of BMC, as taught by US Patent '708 and administration of the bone marrow cells via the hepatic portal vein to provide an improved method for inducing immunological tolerance in an organ transplantation recipient, as taught by Zhang et al., with a method of inducing immunological tolerance in an organ transplantation recipient, taught by US Patent '782. Finally, given the art recognized time constraints associated with transplanting cells and organs from the same human donor; one of ordinary skill in the art would have also been motivated to transplant the organ within the same day as the whole bone marrow cells. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144. Further, it has been held that where the general conditions of a claim are disclosed in the prior art,.discovering the optimum or workable ranges involves only routine skill in the art. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A

message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MICHAIL BELYAVSKYI, PH.D.
PATENT EXAMINER

08/06/07